Non-Melanoma Skin Cancers: Advances in Immunotherapy

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UNIVERSITY of WASHINGTON

Seattle Cancer Care Alliance

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Disclosures

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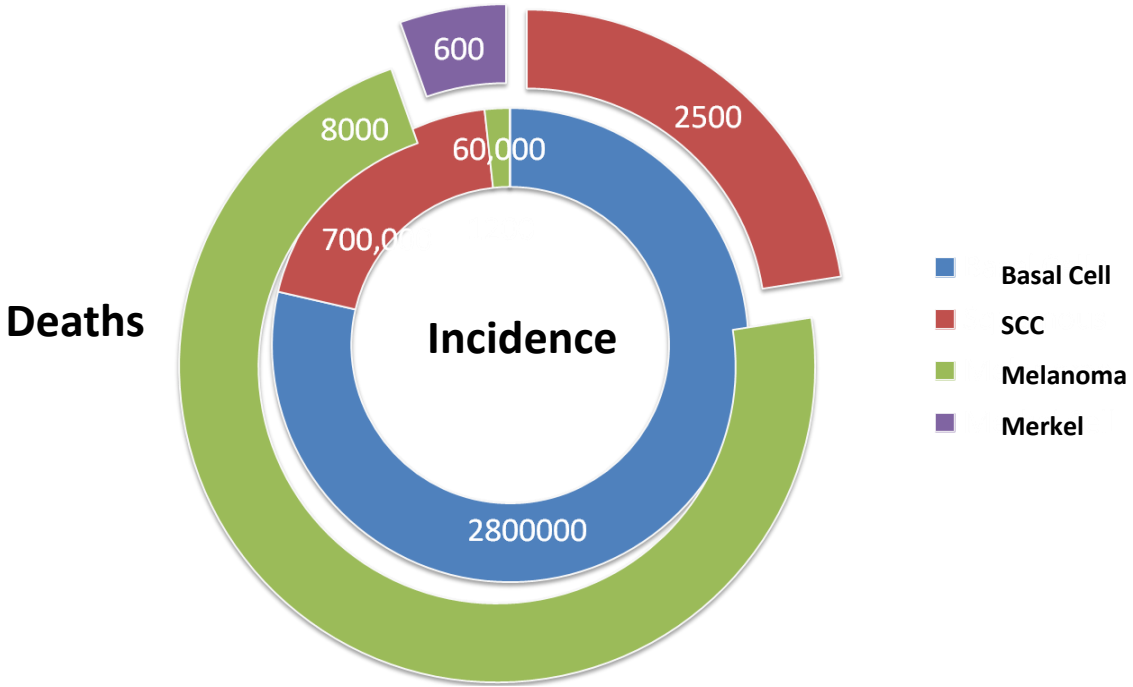
- **Advisory Board**: Genentech, EMD-Serono, BMS (received honoraria)
- **Speaker**: None

Skin, the largest organ, is also the most vulnerable to cancer development



NOTE: The numbers listed in this figure do not reflect the most up-to-date statistics.

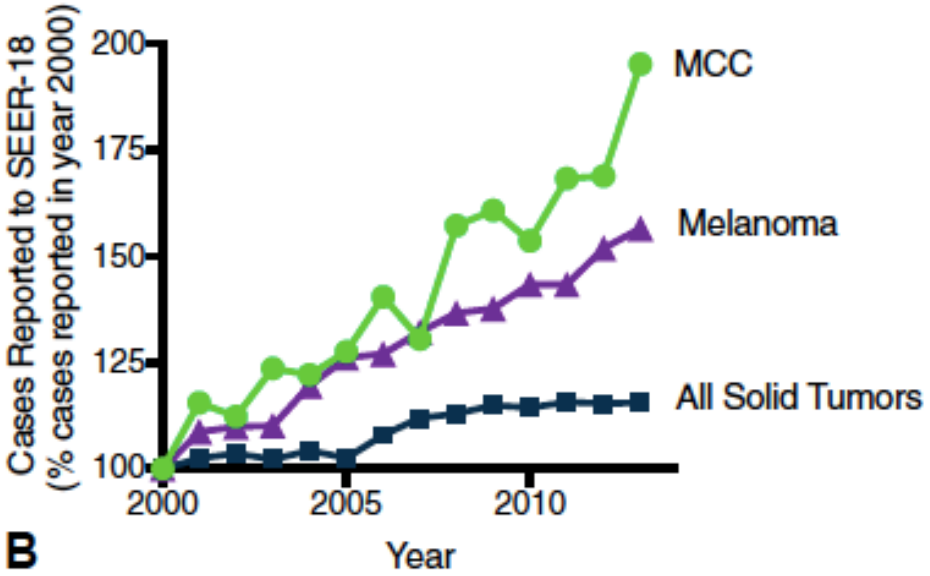
Non-melanoma Skin cancers (NMSCs)

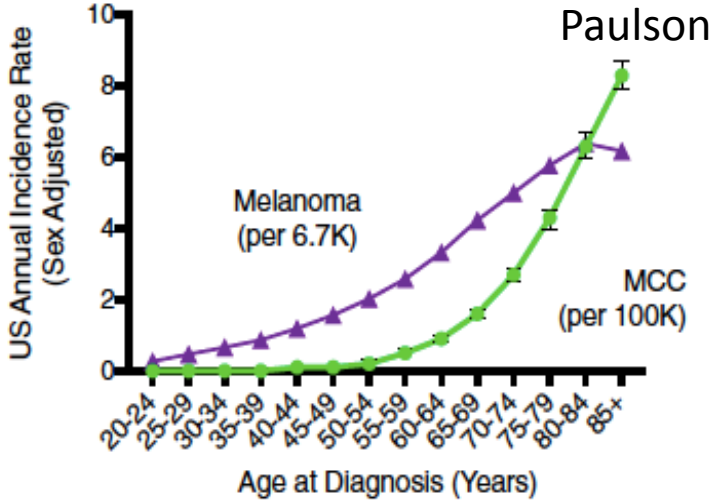
- 5.4 Million diagnosed in 2012
- 3.3 Million treated
  - 80% BCCs
  - 20% cSCC
  - <1% others (including MCC)

{Rogers HW et al. *JAMA Dermatol*. 2015}

Alarming increase in MCC incidence

Kelly Paulson



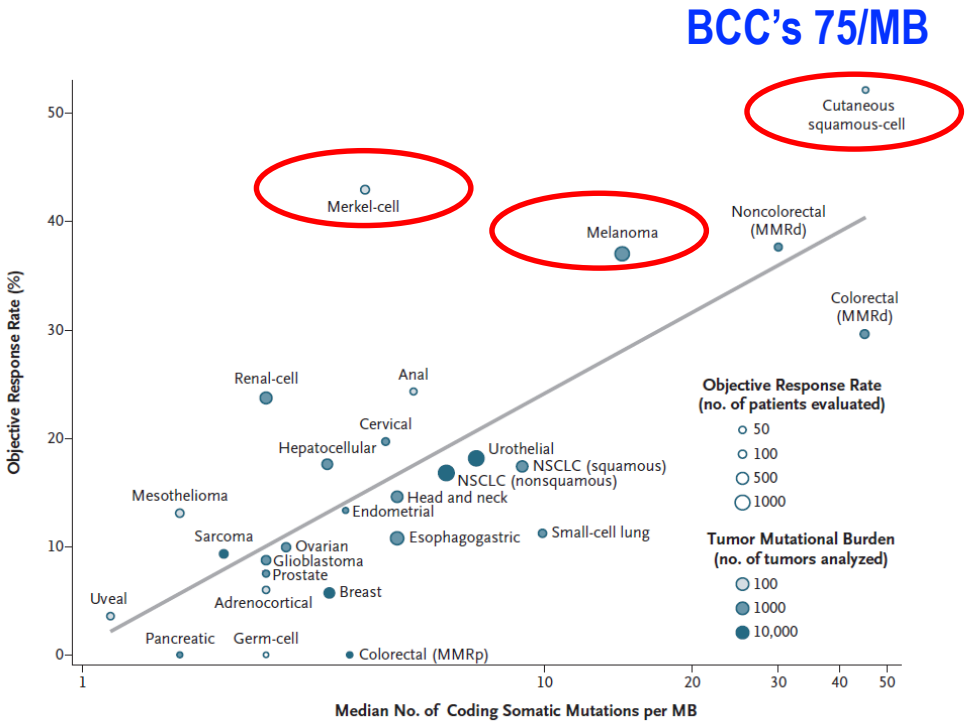


Incidence rate by Age

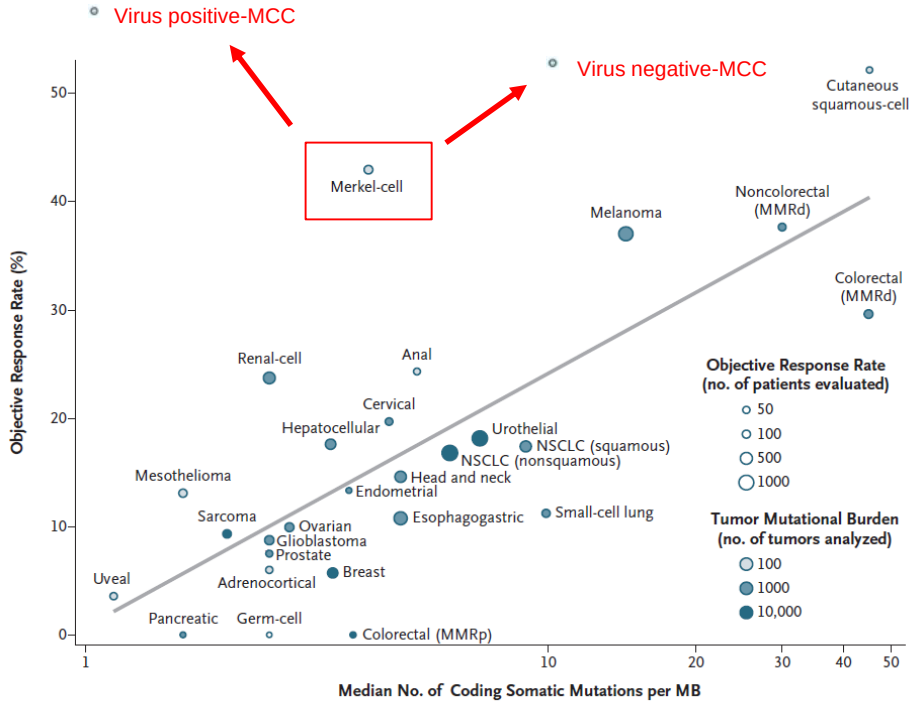
2500 new MCC cases in 2013; estimated ~3300 by the year 2025

{Paulson K et al. *J Am Acad Dermatol*. 2017}

Tumor Mutational Burden (TMB) is generally high in NMSCs: Rationale for immunotherapy

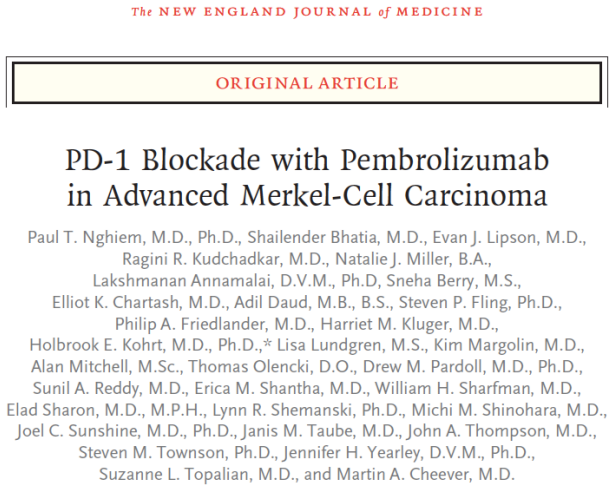


Yarchoan, et al, NEJM 2017
Harms, et al, CA Res, 2015
Jayaraman SS JID 2014



Paulson, et al, unpublished

Remarkable success of PD-1/PD-L1 blockade in MCC



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma

Paul T. Nghiem, M.D., Ph.D., Shailender Bhatia, M.D., Evan J. Lipson, M.D., Ragini R. Kudchadkar, M.D., Natalie J. Miller, B.A., Lakshmanan Annamalai, D.V.M., Ph.D, Sneha Berry, M.S., Elliot K. Chartash, M.D., Adil Daud, M.B., B.S., Steven P. Fling, Ph.D., Philip A. Friedlander, M.D., Harriet M. Kluger, M.D., Holbrook E. Kohrt, M.D., Ph.D.,* Lisa Lundgren, M.S., Kim Margolin, M.D., Alan Mitchell, M.Sc., Thomas Olencki, D.O., Drew M. Pardoll, M.D., Ph.D., Sunil A. Reddy, M.D., Erica M. Shantha, M.D., William H. Sharfman, M.D., Elad Sharon, M.D., M.P.H., Lynn R. Shemanski, Ph.D., Michi M. Shinohara, M.D., Joel C. Sunshine, M.D., Ph.D., Janis M. Taube, M.D., John A. Thompson, M.D., Steven M. Townson, Ph.D., Jennifer H. Yearley, D.V.M., Ph.D., Suzanne L. Topalian, M.D., and Martin A. Cheever, M.D.

Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial

Lancet Oncol 2016

Published Online September 1, 2016 http://dx.doi.org/10.1016/S1470-2045(16)30364-3

See Online/Comment http://dx.doi.org/10.1016/S1470-2045(16)30441-7

Howard L Kaufman, Jeffery Russell, Omid Hamid, Shailender Bhatia, Patrick Terheyden, Sandra P D'Angelo, Kent C Shih, Michele Milella, Isaac Brownell, Karl D Lewis, Jochen H Lorch, Kevin Chin, Lisa Mahnke, Anja von Heydebreck, Jean-Marie

2018 Nobel Prize in Medicine report mentions MCC:

The tumors that show the highest frequency of responses (50-90%) are Hodgkin´s lymphoma especially in patients with overexpression of PD-L1 and PD-L2 caused by gene amplification (Ansell et al., 2015), Merkel cell carcinoma of the skin, being of viral origin (Nghiem et al., 2016), in microsatellite-instability cancers of any origin having high mutational load from mismatch-repair deficiency (Le et al., 2017) and in desmoplasmic melanoma carrying numerous, UV-induced mutations (Eroglu et al., 2018).

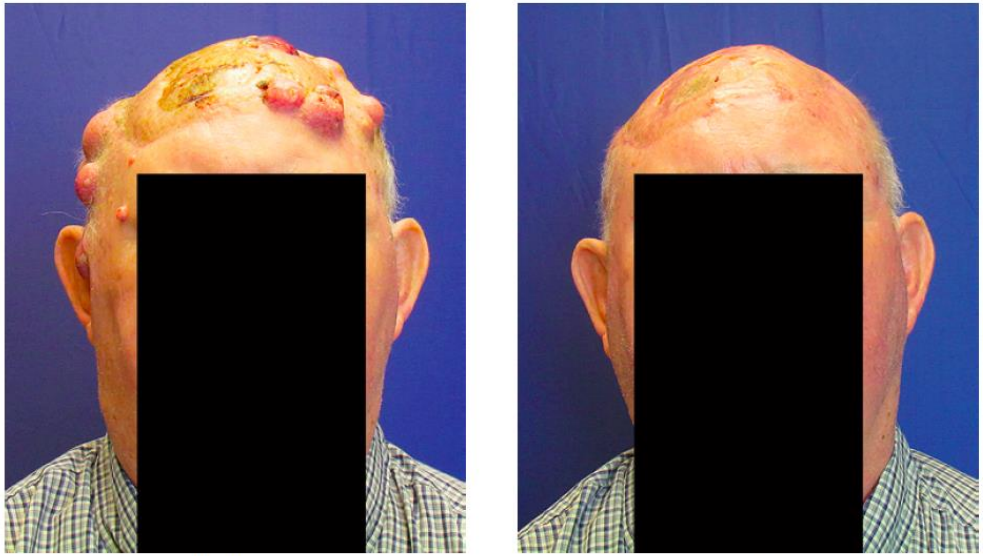
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma

M.R. Migden, D. Rischin, C.D. Schmults, A. Guminski, A. Hauschild, K.D. Lewis, C.H. Chung, L. Hernandez-Aya, A.M. Lim, A.L.S. Chang, G. Rabinowits, A.A. Thai, L.A. Dunn, B.G.M. Hughes, N.I. Khushalani, B. Modi, D. Schadendorf, B. Gao, F. Seebach, S. Li, J. Li, M. Mathias, J. Booth, K. Mohan, E. Stankevich, H.M. Babiker, I. Brana, M. Gil-Martin, J. Homsi, M.L. Johnson, V. Moreno, J. Niu, T.K. Owonikoko, K.P. Papadopoulos, G.D. Yancopoulos, I. Lowy, and M.G. Fury

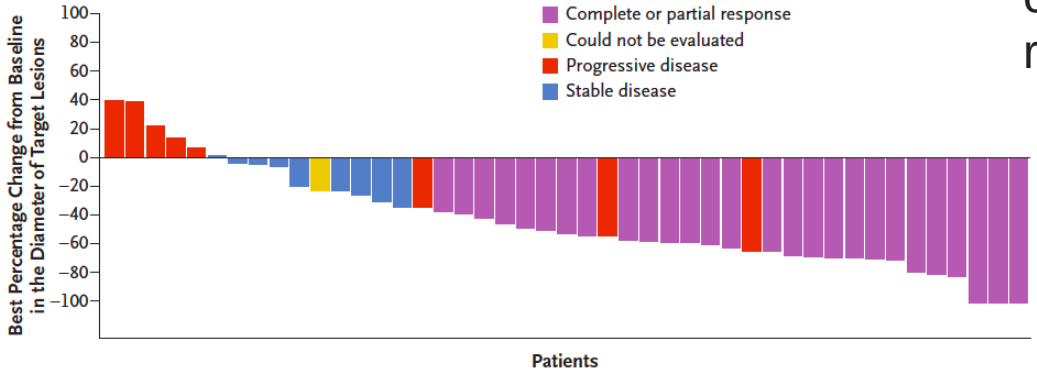
A Patient in Phase 1 Study



Baseline

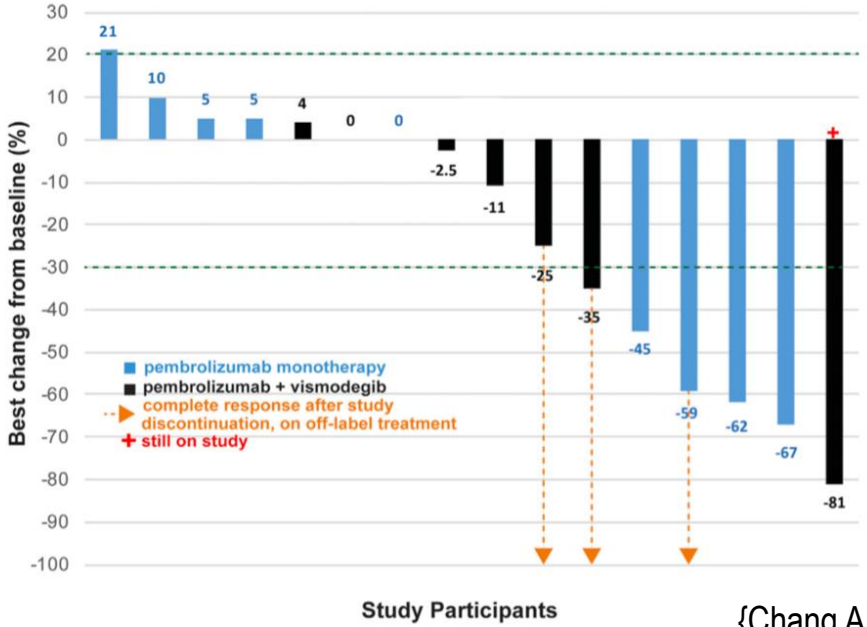
Week 6

A Best Tumor Response for 45 Patients in the Phase 2 Study



On September 28, 2018, the US Food and Drug Administration (FDA) **approved cemiplimab**-rwlc (Libtayo; Regeneron/Sanofi US) for the treatment of patients with locally advanced or metastatic CSCC who are not candidates for curative surgery or curative radiation.

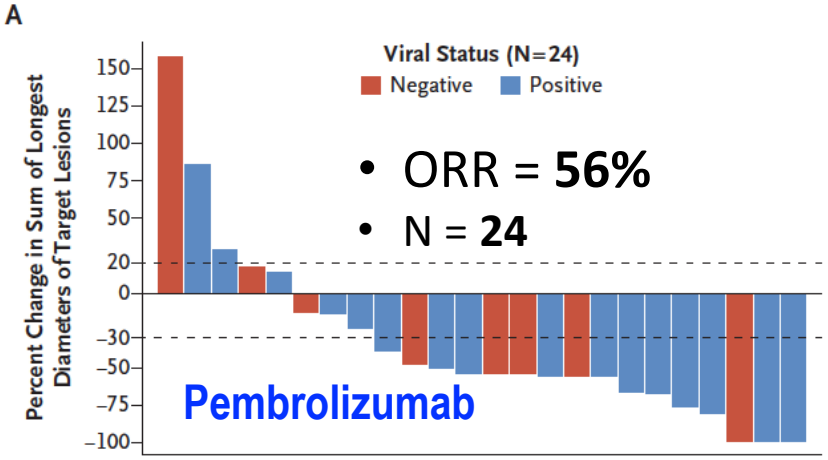
Pembrolizumab for advanced basal cell carcinoma: An investigator-initiated, proof-of-concept study



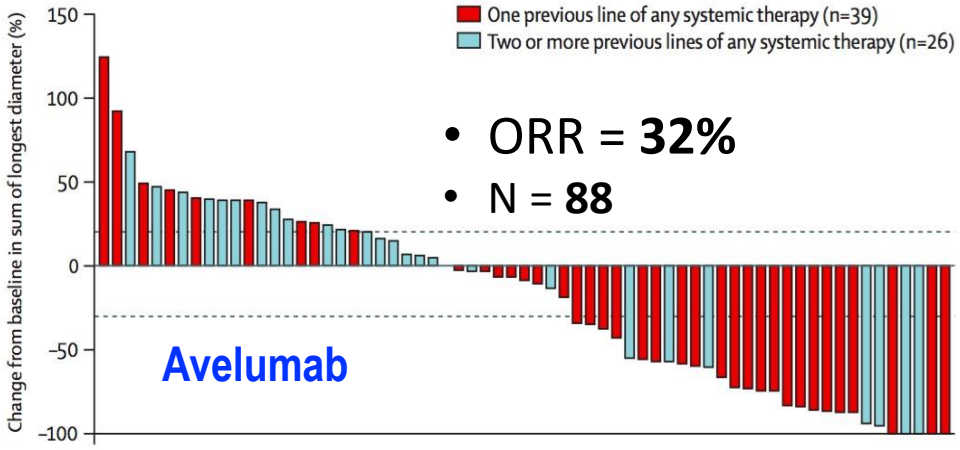
{Chang ALS *JAAD* 2019}

Emerging Data in Merkel cell carcinoma (MCC): Lessons for NMSCs (and even Melanoma)

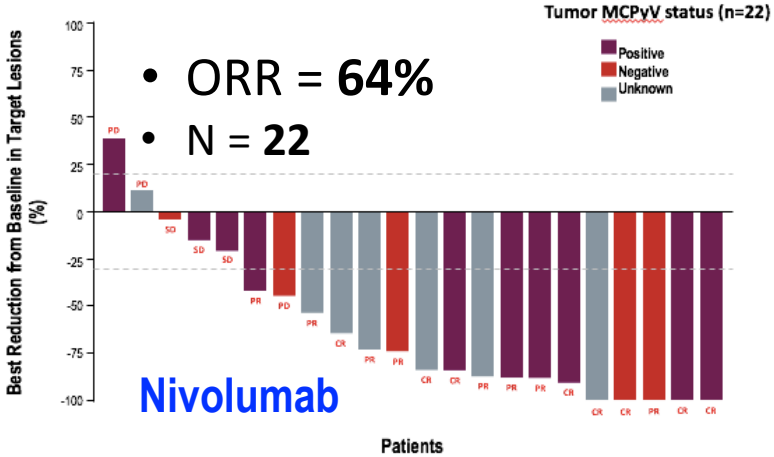
High response rates with ICIs in MCC



- ORR = **56%**
- N = **24**



- ORR = **32%**
- N = **88**



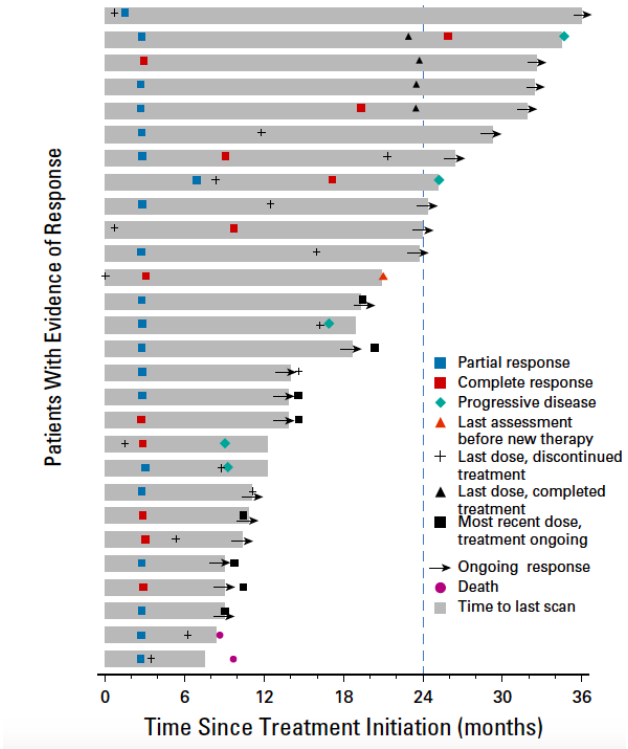
- ORR = **64%**
- N = **22**

{Nghiem P, Bhatia S et al. 2016 *NEJM*}

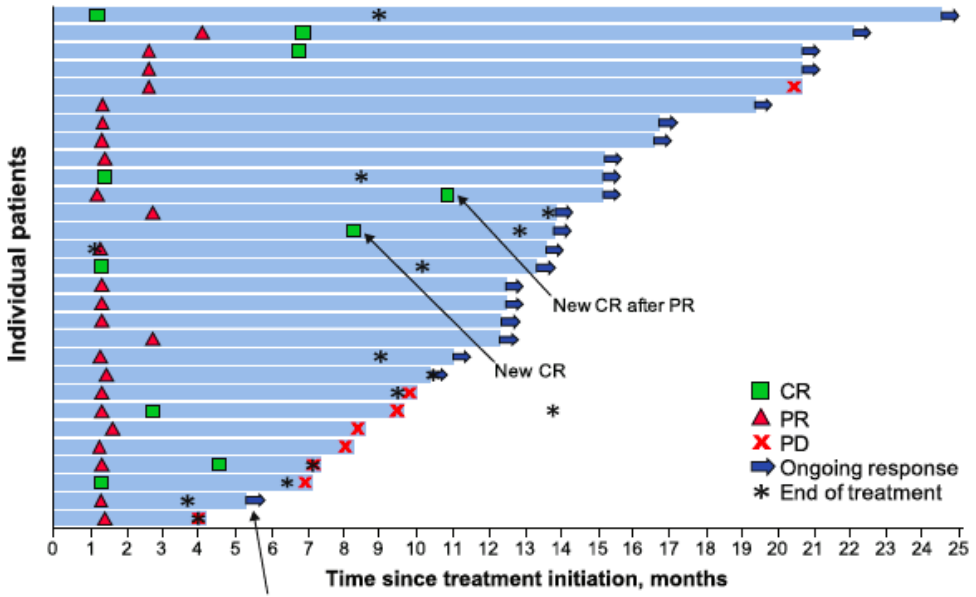
{Kaufman H et al. *The Lancet Oncology* 2016}

{Topalian S, Bhatia S et al. *AACR* 2017}

Unlike chemotherapy, ICI responses are impressively durable

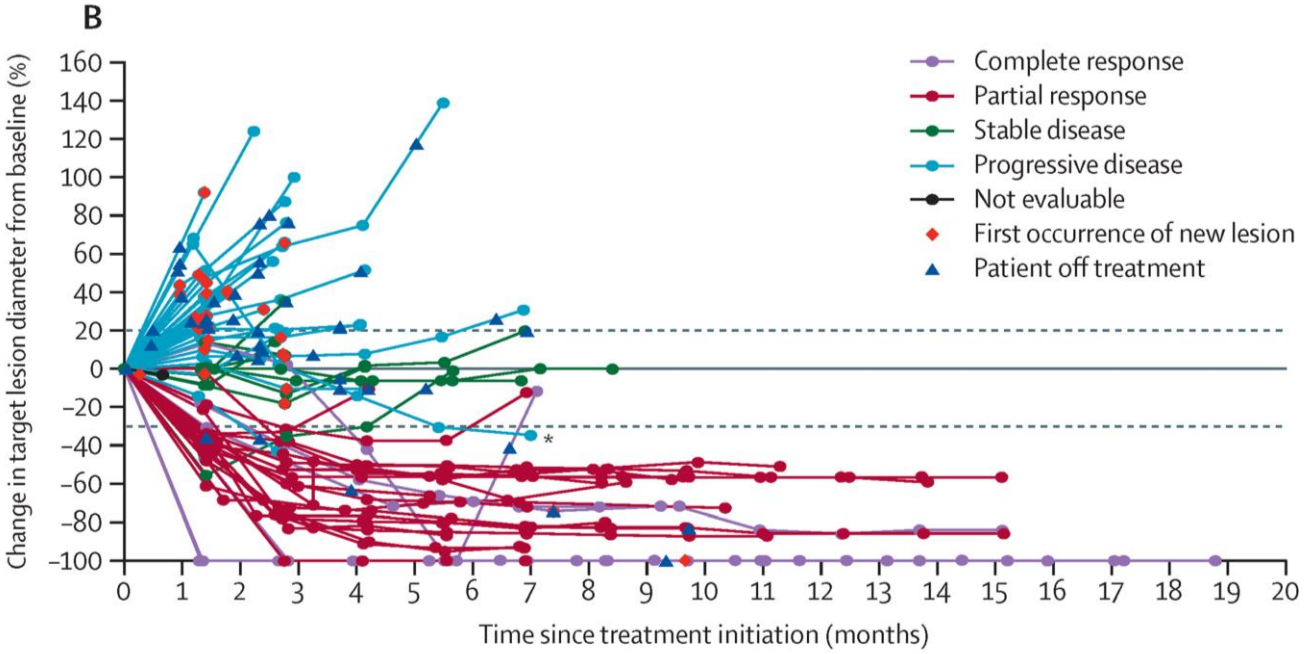


{Nghiem P, Bhatia S et al. 2019 *JCO*}



{Kaufman H et al. *JITC* 2018}

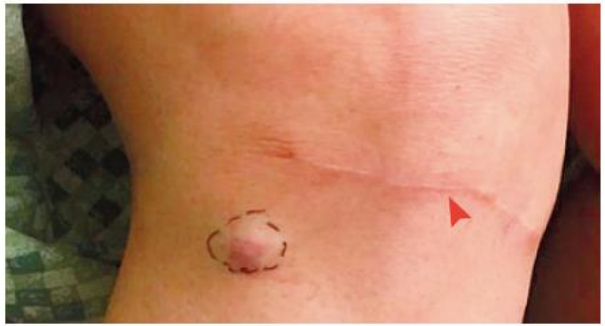
Responses to ICIs are generally rapid-onset



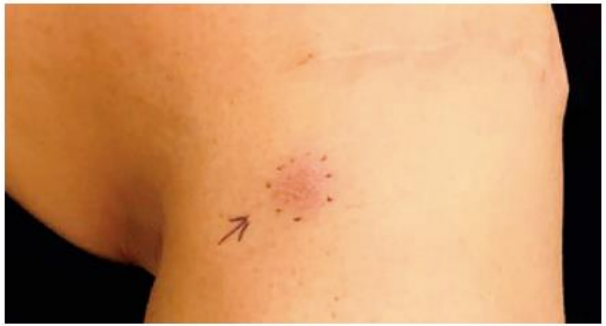
Median time to respond was 6 weeks (time of 1st scan)

{Kaufman H et al. *The Lancet Oncology* 2016}

Rapid response to Pembrolizumab

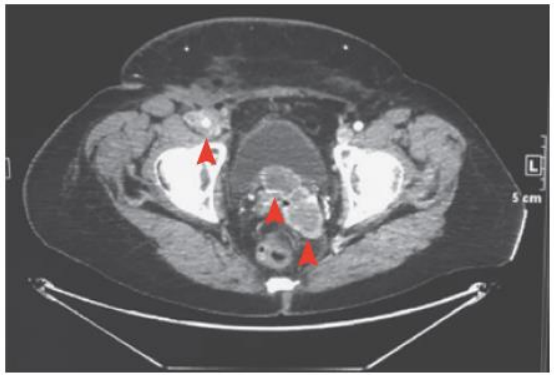


Baseline

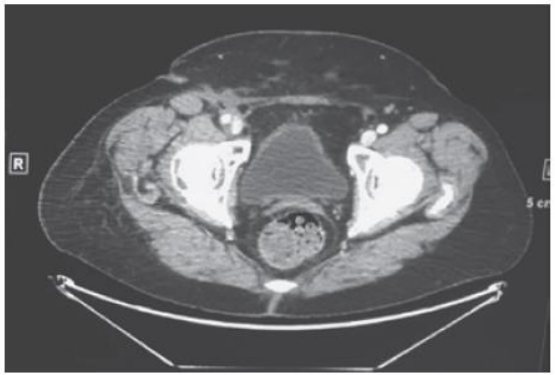


3 Wk

- 69 years old female
- MCPyV+ve tumors
- Chemotherapy-naive



Baseline



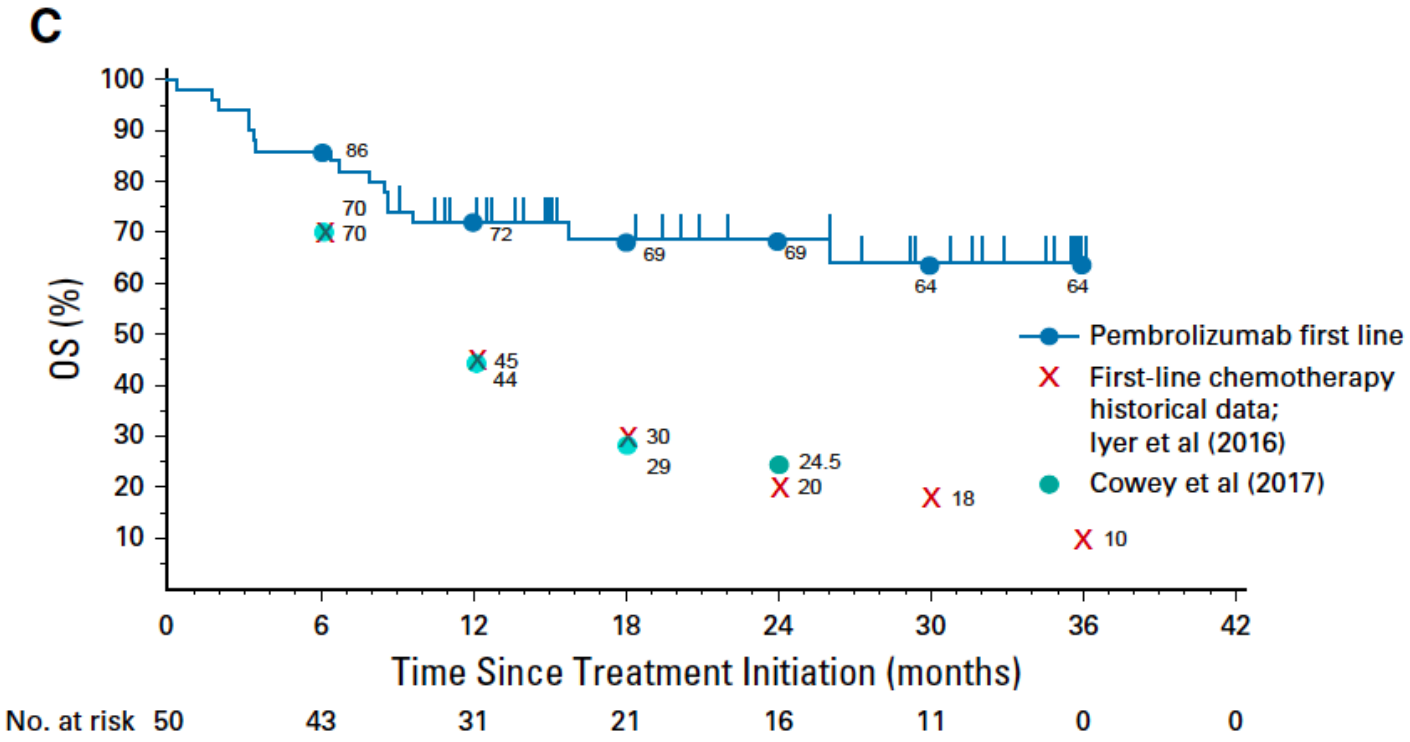
12 Wk

{Nghiem P, Bhatia S et al. 2016 *NEJM*}

Are we meeting our goals for advanced MCC pts with ICIs?

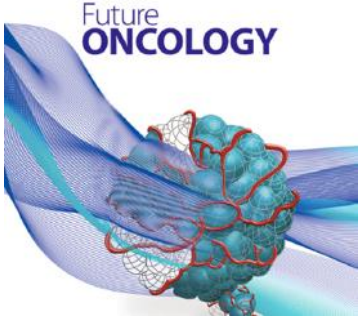
- **CURE**
- Improve overall survival (OS)
- Improve/preserve Quality of life (QoL)

Impact of ICIs on OS in MCC patients



{Nghiem P, Bhatia S et al. 2019 *JCO*}

Nonprogression with avelumab treatment associated with gains in quality of life in metastatic Merkel cell carcinoma



Howard L Kaufman[1], Matthias Hunger[2], Meliessa Hennessy[3], Michael Schlichting[4] & Murtuza Bharmal*,[4]

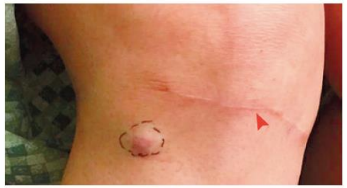
mated. **Results:** Tumor shrinkage correlated positively with patients' change from baseline in the FACT-M total (0.364 [95% CI: 0.050–0.607]) and subscale scores. Differences in HRQoL and utility between nonprogressive disease and progressive disease were clinically relevant. **Conclusion:** In patients with metastatic Merkel cell carcinoma, nonprogression during treatment with avelumab correlated with gains in HRQoL.

Future Oncol. (2018) 14(3), 255–266

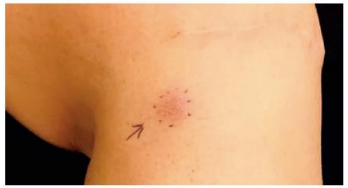
Are we curing MCC patients with ICI?

Our work is not quite done, even in responders!!

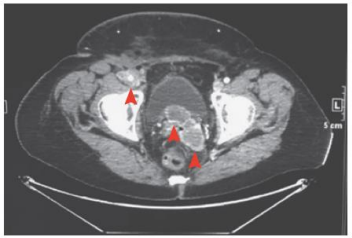
Anecdotal reports of progression in ICI responders are emerging.



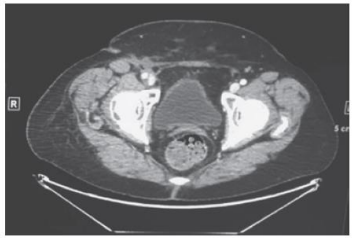
Baseline



3 Wk

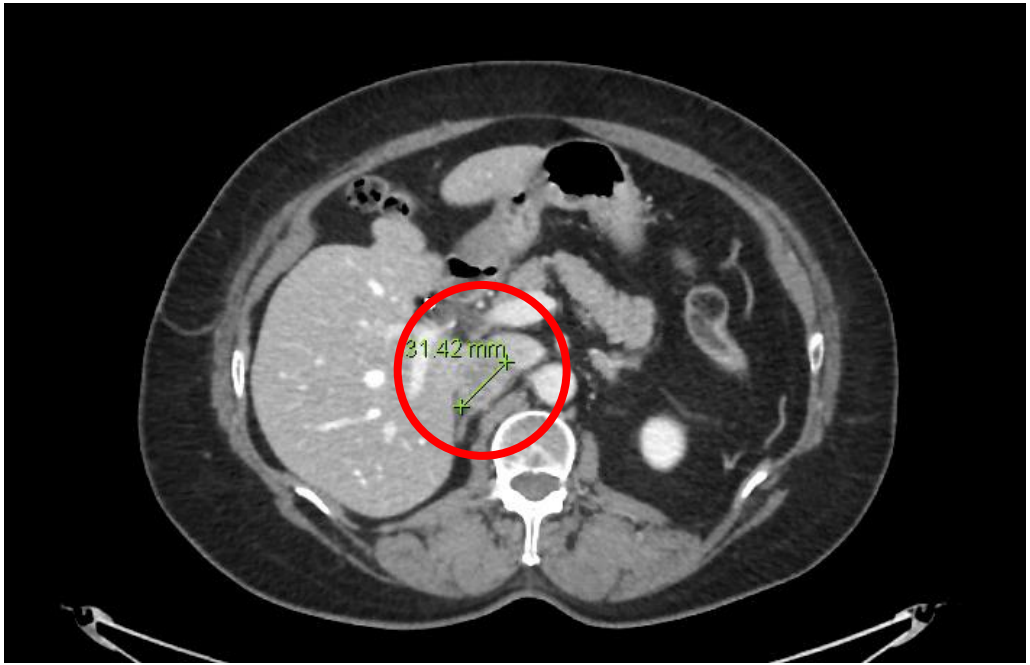


Baseline



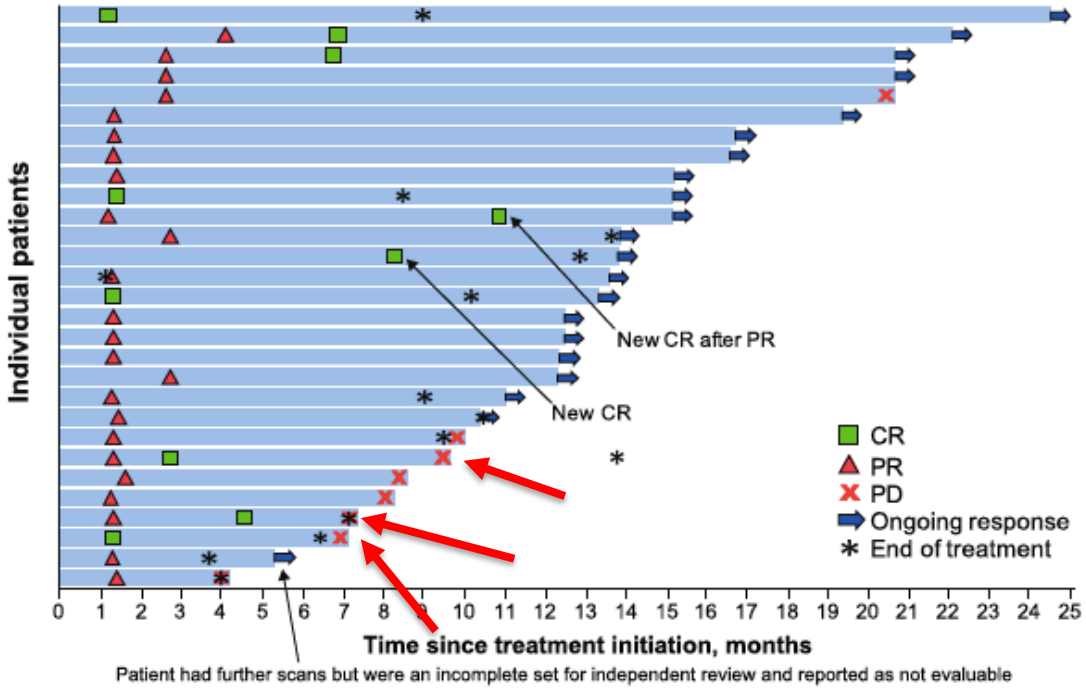
12 Wk

{Nghiem P, Bhatia S et al. 2016 *NEJM*}



3 years later (1 year after last pembrolizumab infusion)

Emerging LTFU data on avelumab trial



ORR only 33%

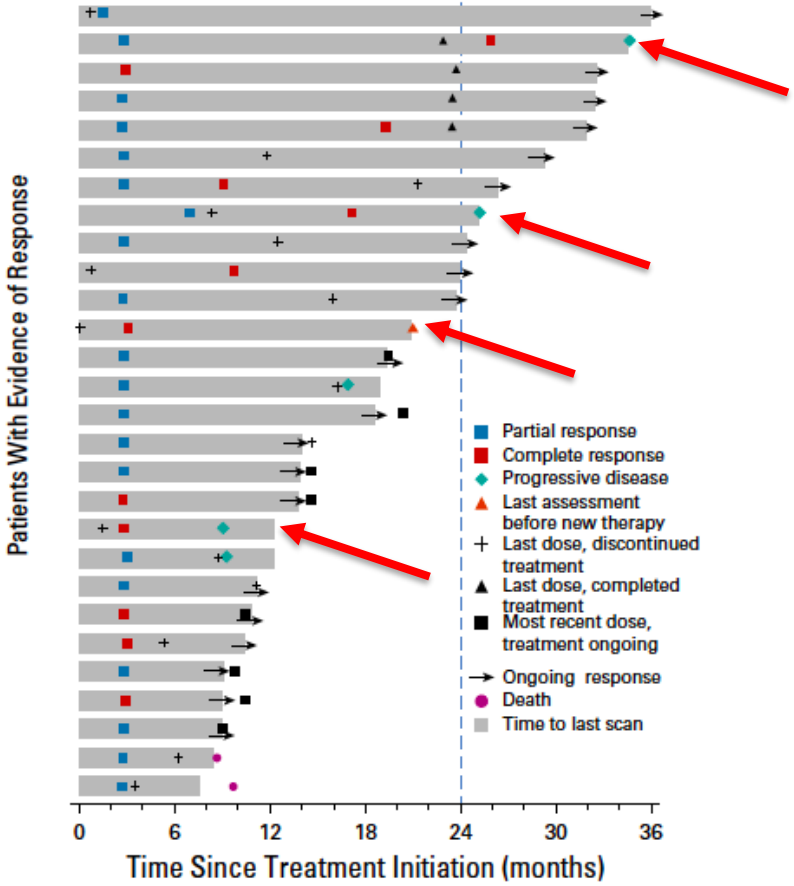
8/29 (**28%**) of responders have progressed

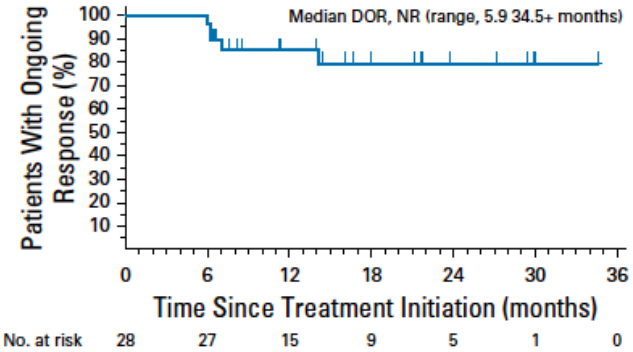
- Majority progressed while still receiving treatment
- Majority progressed in the first year, but delayed progression has also been seen

CR rate only 11%; **3 of 10 (30%) patients with CR progressed**

{Kaufman H et al. *JITC* 2018}

LTFU data in pembrolizumab study

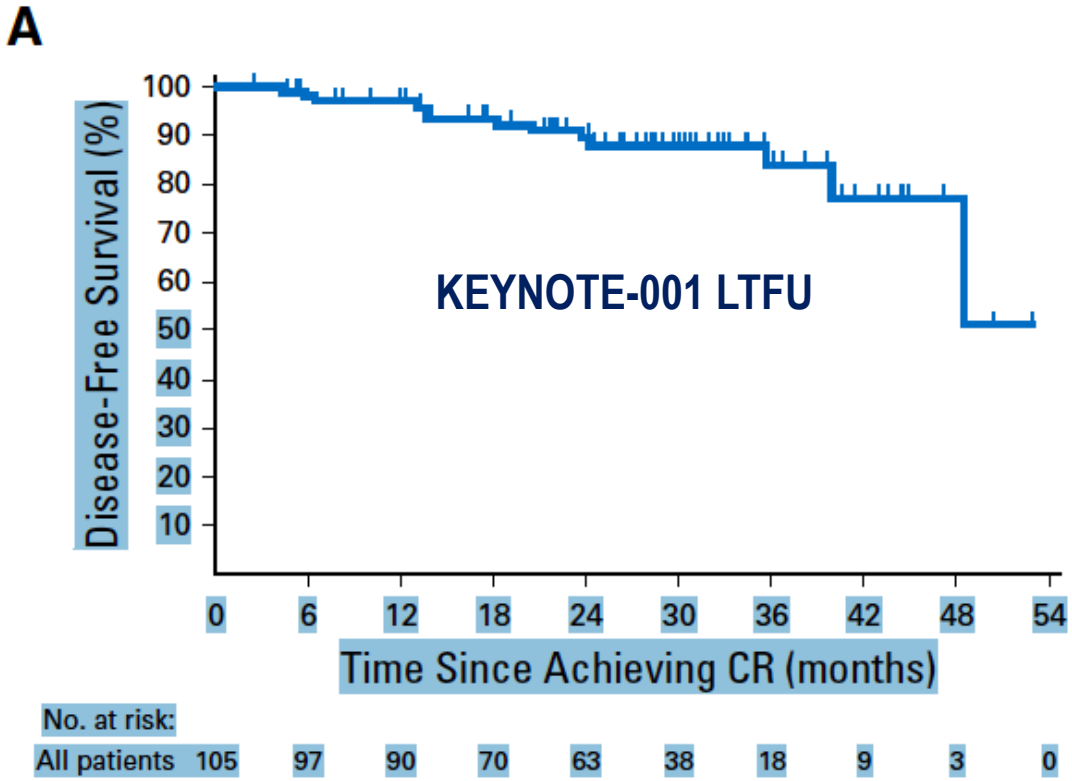




- ORR 56% (28/50)
- 20/28 (**72.4%**) responses ongoing; median F/U ~15 mos
- 12/50 (**24%**) patients with CR
  - **8/12 (66%) CRs ongoing** at last F/U

{Nghiem P, Bhatia S et al. 2019 *JCO*}

How does this compare with melanoma experiences?



CR rate = 105/655 (**16%**)

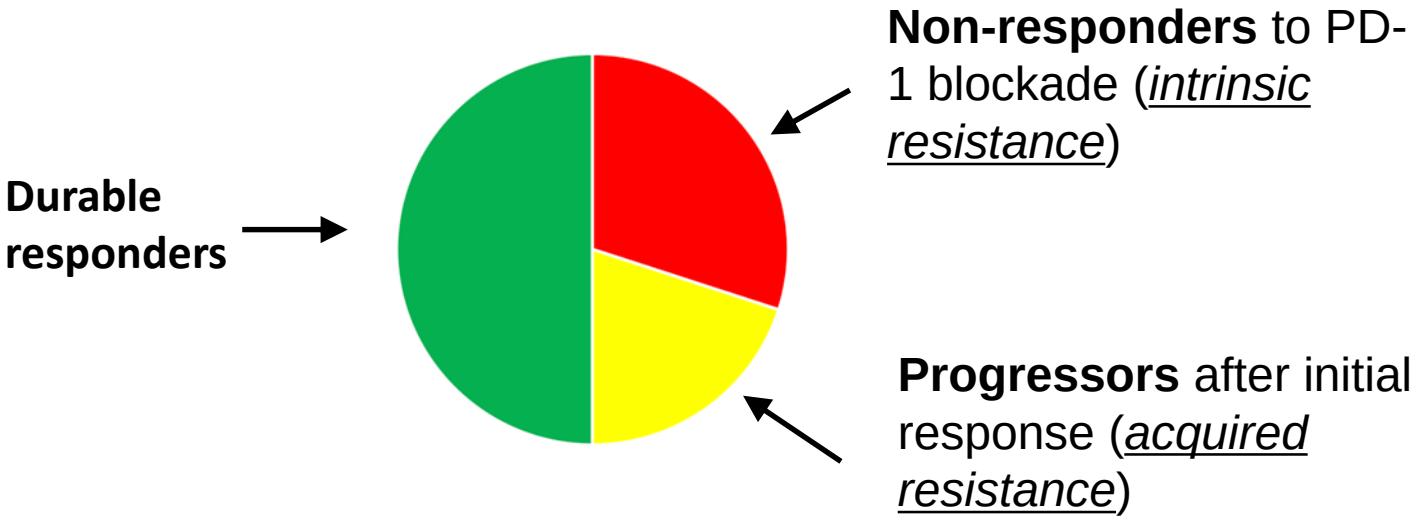
Only 7 of 105 (**6.7%**) had PD at data cutoff

MCC experience so far:

- PD in 4/12 (**33%**) pembro
- PD in 3/10 (**30%**) with avelumab

{Robert C, Ribas A et al. 2018 *JCO*}

3 distinct populations with unmet needs have emerged

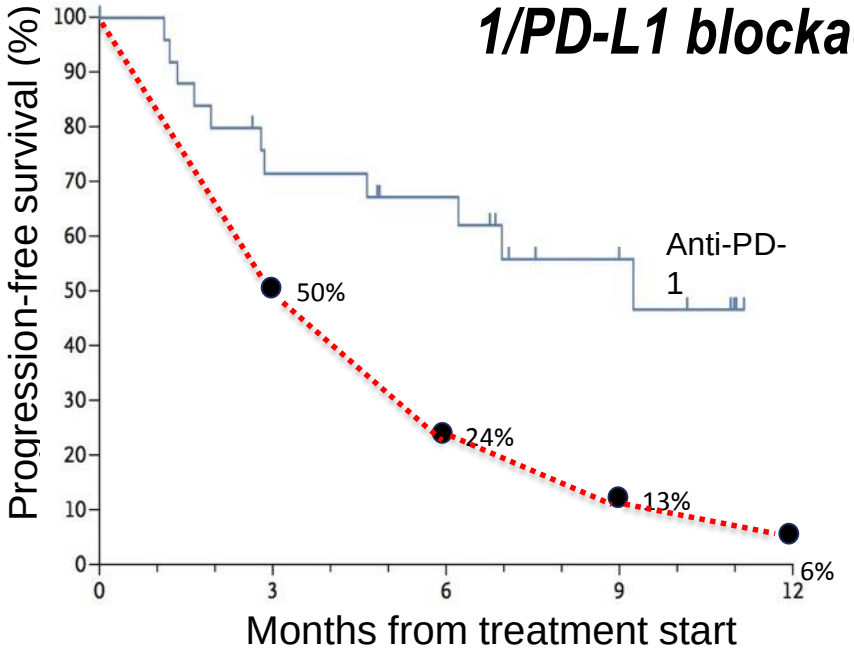


- **Ineligible** patients with *contra-indications* to PD-1 blockade: Immune-suppressed patients; Auto-immune conditions etc.

What can we do to help improve the chances of curing MCC patients?

I. Think critically before choosing chemotherapy over immunotherapy

Is there a reason to choose chemotherapy over PD-1/PD-L1 blockade in immune competent patients?



{Nghiem P, Bhatia S et al. 2016 *NEJM*}

Chemotherapy historical data, (n=62)
{Iyer, et al, Cancer Med 2016}

ORR by number of prior Chemo regimens:

0 ~ 60%
1 ~ 40%
≥2 ~ 20%

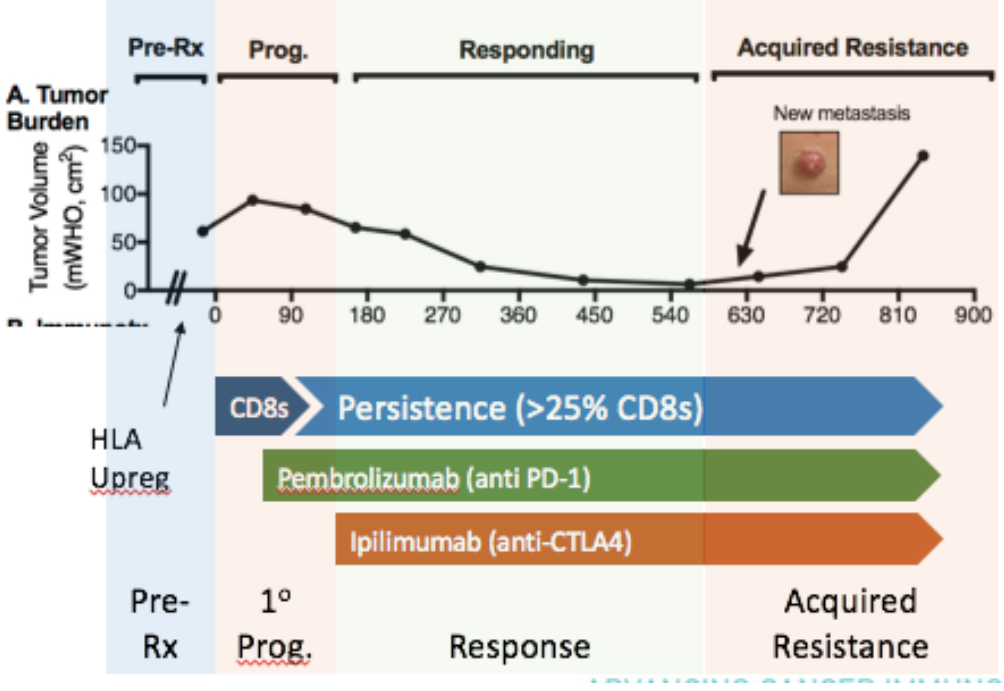
Caution: Numbers are rounded and from separate trials

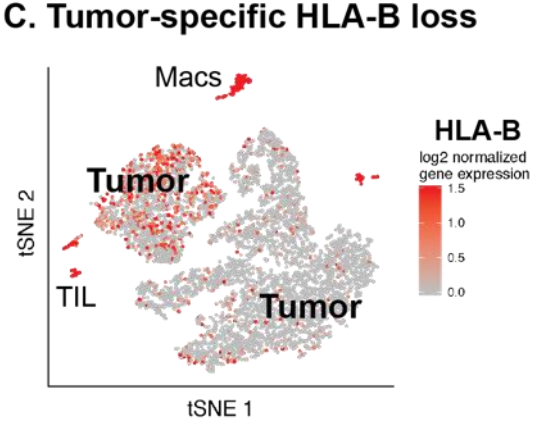
{Kaufman H et al. *The Lancet Oncology* 2016}

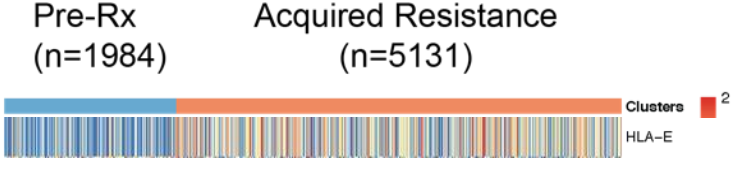
{Topalian S, Bhatia S et al. *AACR* 2017}

II. Uncover mechanisms of intrinsic and acquired resistance

Patient had received **HLA-B*3502 restricted CD8s** targeting MCPyV







Kelly Paulson

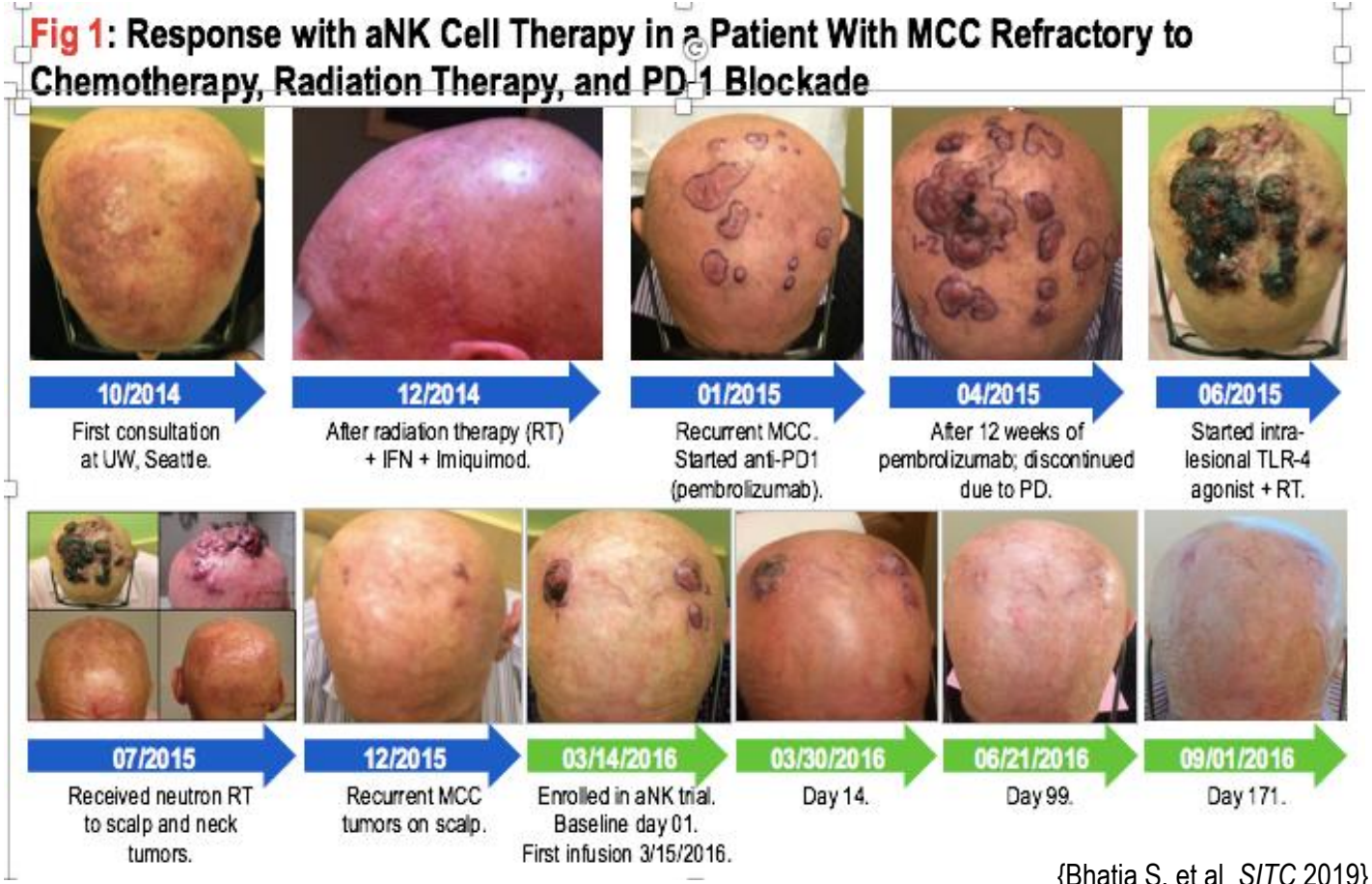
{Paulson K, et al…Chapuis A. *SITC* 2017}

III. Prioritize **Clinical trials** for ICI-resistant MCC!!

Numerous strategies being investigated in refractory MCC (too many to summarize in this talk)

- Intra-lesional approaches [TVEC; TTI-621; STING-agonist; several TLRs]
- Cellular therapies [aNK-cells; MCPyV-TCR (ATTAC-MCC)]
- Immune-checkpoints and costimulatory agonists [CTLA-4; 41bb]
- Others [MDM2i; cytokines (NKTR-214, ALT-803); SSTR-PRRT; Radiation]

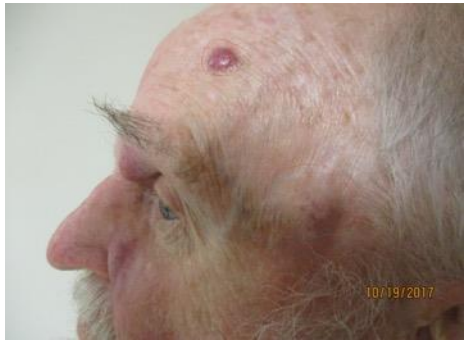
Reversal of ICI-refractoriness with NK cells



{Bhatia S, et al *SITC* 2019}

Abscopal response to Neutron RT in a patient with CLL and MCC progressing on pembrolizumab

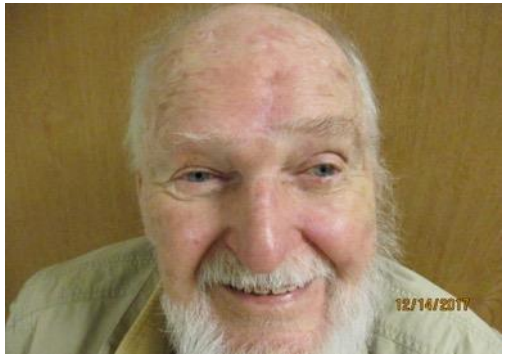
Upendra Parvathaneni
Rad Onc, UW

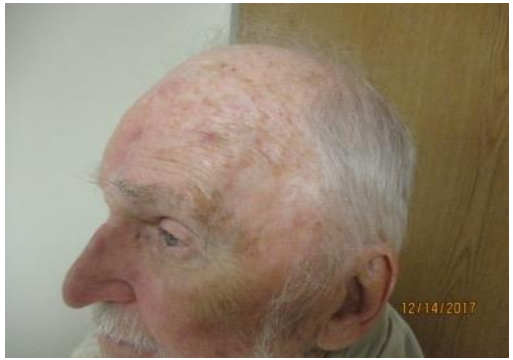


10/12/2017

Neutron RT

Continued pembrolizumab





12/14/2017

IV. Use Adjuvant systemic therapy for high-risk NMSC

ADjuvant Avelumab in Merkel (ADAM)

- First ever Phase 3 RCT in MCC; NCT#03271372
- **N=100;** Avelumab versus **Placebo** (1:1)
- **Very high-risk MCC (clinically-detected LN mets)**
- RFS is[32] the primary endpoint
- FPFV occurred in 12/2017

Investigator-initiated (PI: Bhatia)
Funding Sponsor: EMD-Serono
Multi-center; 10 centers in the US

EA6174: An ECOG-ACRIN adjuvant MCC trial

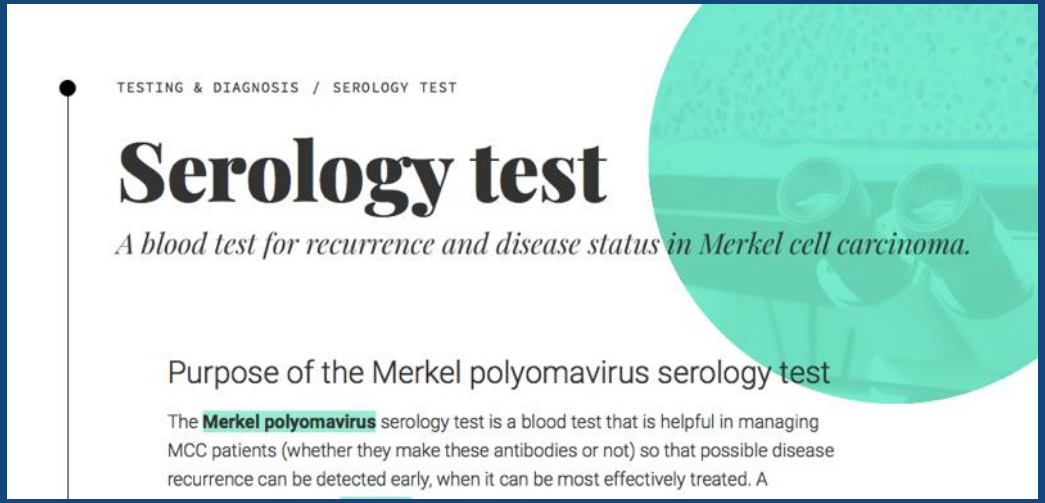
- NCT03712605; activated in October 2018
- PI – Brian Gastman/Charles Hsu
- Stages I (no SLNB)-III
- Pembrolizumab vs observation
- N=500; Phase 3

Pembrolizumab Versus Placebo Following Surgery and Radiation in Participants With Locally Advanced Cutaneous Squamous Cell Carcinoma (MK-3475-630/KEYNOTE-630)

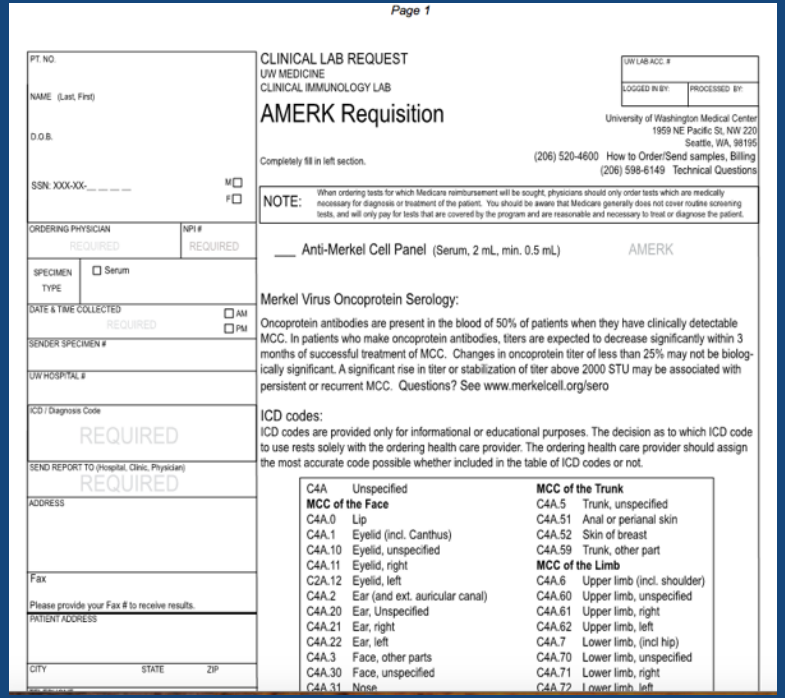
- N=570
- Histologically confirmed LA cSCC with ≥1 high-risk feature(s) as the primary site of malignancy

V. Early detection of recurrences using surveillance

Serologic Surveillance for relapse (AMERK):
a validated, clinically available test listed in the NCCN guidelines



https://merkelcell.org/testing-and-diagnosis/sero/



CONCLUSIONS

- NMSCs are rising in incidence with a growing impact
- High-mutational burden and viral associations (MCC) contribute to immmunogenicity
- Data with PD-1 blockade look highly promising, with frequent and durable responses
- Immunotherapy should be considered for front-line systemic therapy of NMSCs, when feasible and appropriate.

We still have lots of work to do!

Let us not celebrate too much too soon!

The New York Times

OP-ED CONTRIBUTOR

Clinical Trials Need Cancer Patients

By Stan Collender

June 19, 2015

Stan Collender

Tuesday, September 3, 2019

A TRIBUTE TO STAN COLLENDER: THE BUDGET GUY, IMMUNOTHERAPY PIONEER (PATIENT #1), COLLEAGUE AND FRIEND (1951-2019)

By Michael B. Atkins, MD